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CASE REPORT

Breast cancer after bilateral subcutaneous mastectomy in a female-to-male trans-sexual

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SUMMARY. We describe a female-to-male trans-sexual, aged 33, who developed breast cancer 10 years after cosmetic bilateral subcutaneous mastectomy and nipple reimplantation. The complex hormonal pathways involved and the implications for women undergoing prophylactic mastectomy because of a high risk of familial breast cancer are discussed. © 2003 Elsevier Science Ltd. All rights reserved.

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CASE REPORT

This female-to-male trans-sexual with a history of childhood gender identity problems and cross-dressing commenced testosterone supplements to induce masculinization aged 20. Three years later he underwent cosmetic bilateral subcutaneous mastectomy with nipple reimplantation.

He presented with a painless left areola mass aged 33. FNA cytology confirmed carcinoma and subsequent staging chest X-ray and liver function tests were normal. A completion left mastectomy and level II axillary node clearance was performed. Histological examination revealed a completely excised 11 mm grade I node negative (0/13 nodes) oestrogen and progesterone receptor positive ductal carcinoma, infiltrating the underlying pectoralis muscle (pT4aN0M0). The nipple was normal.

Clinical examination revealed female genitalia with signs of masculinization and clitoromegaly. Hormone profile studies confirmed satisfactory androgen replacement (normal testosterone with LH and FSH suppression) and an oestradiol level (E2) within the normal female follicular phase reference range.

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He received adjuvant Tamoxifen (20 mg daily) and post-operative chest-wall irradiation (40 Gy in 15 daily fractions over 21 days). Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed to render the patient post-menopausal and eliminate any subsequent risk of iatrogenic endometrial carcinoma. After 5 years regular clinical follow-up, he remains free of recurrence on transdermal dihydrotestosterone replacement therapy.

DISCUSSION

This case of breast cancer in a female-to-male trans-sexual exposed to exogenous androgens is unique in the medical literature. As well as demonstrating the complex and poorly understood hormonal influences involved in the aetiology of breast cancer, this patient's management raises some important clinical issues. The potential causative role of androgen replacement in breast malignancy, and the benefits, risks and safety of such treatment in breast cancer survivors are discussed. The protection afforded to high-risk women undergoing prophylactic mastectomy is reviewed and the optimal hormonal management of this case is considered.

The precise causative role of androgens in breast cancer aetiology is unclear but the association between high androgen levels and breast cancer risk is well-documented.[1–5] High circulating androgens in post-

menopausal women may increase oestrogens via peripheral aromatization of dihydroepiandrostenedione (DHEA) to oestradiol (E2) and oestrone in breast and adipose tissue. Metabolites of DHEA compete with E2 to stimulate oestrogen receptors (Ers). Prolonged and unopposed oestrogenic stimulation increases breast cancer risk.

Androgen receptors (ARs) are expressed more frequently in breast cancer tissue than (ERs) or progesterone receptors (PgRs).[6] Indeed, a subset of ER and PgR negative breast tumours may express AR only. Direct androgenic stimulation of both AR and ER may therefore be implicated in the regulation of breast tumour growth, though the precise mechanisms and pathways involved are unknown.[7]

A prospective study[8] of urinary androgen excretion and breast cancer risk in 5000 women in Guernsey showed high urinary androgens were protective in young women but increased relative risk in older cohorts. Wang attempts to explain this apparent contradiction by postulating that the effect of androgens varies with age – inhibiting oestrogens in premenopausal women but enhancing oestrogenic effects after the menopause. High urinary androgens are therefore protective before the menopause but become stimulatory with increasing age. Consequently, excessive androgen levels initially counteract the effects of oestrogenic stimulation on breast tissue but, as the effect reverses with age, prolonged androgen and oestrogen exposure increases the risk of breast cancer. A similar mechanism may have contributed to the development of breast cancer in this patient after 13 years of exogenous androgen therapy.

A smaller prospective case–cohort study[9] demonstrated that elevated levels of both E2 and testosterone increase breast cancer risk significantly. Amongst 97 cases and 244 matched controls, the relative risk of breast cancer in women with increased E2, testosterone, or both was 3.6, 3.3 and 6.5, respectively. Consequently, the combination of a normal female follicular E2 level in the presence of satisfactory androgen replacement in this patient increases the chance of breast cancer by at least three-fold. Clearly, any female-to-male trans-sexual requesting androgen supplements must be made aware of the increased risk arising from such treatment.

The potential benefits of prophylactic oophorectomy at the time of initiating androgen supplementation are unknown. Paradoxically, rendering the patient post-menopausal may reduce the relative risk of breast carcinogenesis[9] but, at the same time, any benefit may be offset by the increased risk arising from prolonged unopposed androgens in the post-menopausal state.[8]

Three cases of breast cancer in male-to-female trans-sexuals attributed to exogenous oestrogen replacement therapy have been reported.[10,11] All three patients had also undergone bilateral orchidectomy. However, the safety of androgen replacement in breast cancer survivors is uncertain. The Endocrine Society of Australia consensus guidelines state that breast cancer is a contraindication to androgen therapy,[12] though there is little clinical evidence to support this.

In this rare case, androgen supplementation has been carefully tailored to satisfy the patient's unique and conflicting medical needs. Whilst adequate androgen replacement is necessary to preserve his reassigned gender and masculinity, these benefits must be balanced against the theoretical risk that androgen therapy may promote recurrence of his breast cancer. As a compromise, the patient has been maintained on the lowest exogenous androgen dose that provides acceptable features of masculinity. In addition, transdermal dihydrotestosterone gel (Andractin 2.5% gel, Laboratoire Besius Iscovesko, Paris) has been used in an attempt to minimize circulating testosterone and therefore avoid unnecessary aromatization to E2. Thus far, this strategy has succeeded.

This individual has no known family history of breast cancer and underwent prophylactic mastectomy solely for the purposes of gender reassignment. However, the case has implications for women at high risk of breast cancer considering prophylactic mastectomy and for trans-sexuals undergoing hormonal manipulation and female-to-male sex-change surgery.

Preservation of the nipple areola complex at subcutaneous mastectomy leaves behind insensate ductal tissue at risk of malignant transformation. Total glandular mastectomy (removal of the nipple with preservation of the areola) has been advocated as an alternative[13] but residual breast tissue persists even after the most radical prophylactic surgery.[14] The inability of subcutaneous mastectomy to remove all glandular tissue is a major limitation, particularly in high-risk individuals in whom any residual breast tissue has significant neoplastic potential.

As a result, prophylactic mastectomy does not completely abolish cancer risk and there are many reports of breast cancer developing 3–18 years after prophylactic surgery for benign indications.[15–19] In patients with a hereditary susceptibility to breast cancer, to date there have been no prospective clinical trials assessing the effectiveness of bilateral prophylactic mastectomy preventing subsequent malignancy. A large retrospective series of 639 high-risk women from the Mayo Clinic found that prophylactic mastectomy

afforded a 90% reduction in breast cancer incidence and mortality compared to controls.[20] All of the cancers occurred in women who had undergone subcutaneous mastectomy.

The management pathway for this patient has not differed greatly from that of a similarly aged healthy female with a completely excised small node negative breast cancer. The only departures from conventional treatment are the recommendation that surgical oophorectomy be performed and the careful consideration given to the most appropriate dose and method of administration of androgen replacement.

The rationale for delivering post-operative irradiation is straightforward and evidence-based. Chest-wall irradiation after excision of a locally advanced mass invading the pectoralis muscle significantly reduces the risk of local recurrence.

The optimal hormonal management of this case is more open to debate. Adjuvant Tamoxifen is clearly indicated in view of the oestrogen and progesterone receptor positivity[21] and is not contraindicated with concurrent androgen therapy. However, the role of aromatase inhibitors in this setting is unknown. Inhibition of peripheral aromatization of adrenal androstenedione to E2 minimizes circulating oestrogens in postmenopausal women but the efficacy of aromatase inhibitors in the presence of exogenous androgens, whilst theoretically attractive, has not been studied.[22]

Prophylactic oophorectomy was undertaken since it offered dual potential benefits: induction of an artificial menopause may provide a small survival advantage in premenopausal breast cancer survivors[23] and, at the same time, eliminate any excess risk of endometrial carcinoma in a redundant uterus. The preferred method of oophorectomy was debated in a multidisciplinary setting. Medical oophorectomy using gonadotrophin-releasing hormone analogues, whilst reversible, requires continuous treatment and may complicate androgen replacement. A radiation menopause was avoided in case pelvic fibrosis complicated subsequent sex-change surgery. Consequently, total abdominal hysterectomy and oophorectomy via a Pfannenstiel incision was recommended.

In conclusion, it is impossible to speculate whether this patient would have developed breast cancer had he undergone oophorectomy at the time of initial androgen supplementation or total glandular mastectomy in place of subcutaneous mastectomy. Equally, the magnitude of any additional benefit from adjuvant aromatase inhibition is impossible to quantify, though the 5-year disease-free survival to date is encouraging. However, this unique and interesting case demonstrates the complex hormonal influences involved in the causation and risk of relapse of breast cancer, with particular reference to androgens, and provides a number of important clinical lessons that can be applied to the everyday management of breast cancer.

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